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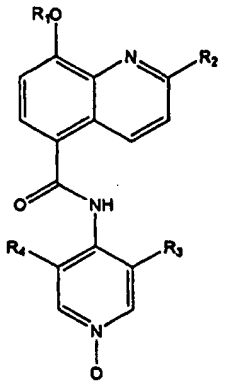

(I)

(57) Abstract

N–oxides of formula (i) wherein R_1 is CH_3, CH_2F, CHF_2 or CF_3; R_2 is CH_3 or CF_3; R_3 is F, Cl, Br, CN or CH_3; and R_4 is H, F, Cl, Br, CN or CH_3; and pharmaceutically–acceptable salts thereof, are useful as therapeutic agents, e.g. for the treatment of inflammatory diseases.

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N-OXIDES OF HETEROCYCLIC COMPOUNDS WITH TNF AND PDE-IV INHIBITING ACTIVITY

The present invention relates to novel heterocyclic compounds and to their formulation and use as pharmaceuticals.

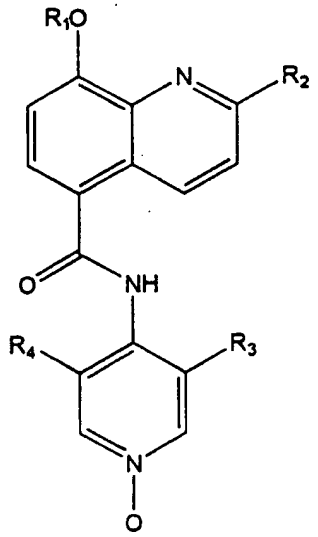
Background of the Invention

EP-A-0498722 describes quinoline derivatives as angiotensin A_2 and endothelin inhibitors.

The modes of action of phosphodiesterases and also tumour necrosis factors (TNF), and the therapeutic utilities of inhibitors thereof, are described in WO-A-9744036 and US Patent No. 5804588, the contents of which are incorporated herein by reference. These publications specifically disclose quinoline carboxamides having such inhibitory activity.

Summary of the invention

This invention provides novel compounds having therapeutic utility, in particular for the treatment of disease states associated with proteins which mediate cellular activity, for example by inhibiting TNF and/or PDE IV. According to the invention, the compounds are of formula (i):



(i)

wherein

R_1 is CH_3, CH_2F, CHF_2 or CF_3;

R_2 is CH_3 or CF_3;

R_3 is F, Cl, Br, CN or CH_3; and

R_4 is H, F, Cl, Br, CN or CH_3;

or a pharmaceutically-acceptable salt thereof.

In summary, the compounds of the invention are N-oxides of the corresponding free bases which are disclosed, some specifically, in WO-A-9744036. The novel compounds have superior solubility, improved metabolic stability, and an improved pharmacokinetic profile. The compound of Example 8 is particularly preferred.

This invention provides also a method for mediating or inhibiting the enzymatic activity or catalytic activity of PDE IV in a mammal in need thereof and for inhibiting the production of TNF in a mammal in need thereof, which comprises administering to said mammal an effective amount of a compound of Formula (i) or a pharmaceutically-acceptable salt thereof.

Brief Description of the Drawing

The accompanying drawing is a graph showing pK data, following oral dosing in the rat, of a compound of the invention and, for comparison, of a known compound.

Description of the Invention

Certain of the compounds of formula (i) which contain a basic group form acid addition salts. Suitable acid addition salts include pharmaceutically-acceptable inorganic salts such as the sulphate, nitrate, phosphate, borate, hydrochloride and hydrobromide, and pharmaceutically-acceptable organic acid addition salts such as acetate, tartrate, maleate, citrate, succinate, benzoate, ascorbate, methanesulphate, α-ketoglutarate, α-glycerophosphate and glucose-1-phosphate. The pharmaceutically-acceptable salts of the compounds of formula (i) are prepared using conventional procedures.

Compounds of the invention may be prepared by N-oxidation of the corresponding free base. The free bases are known, or can be prepared by the processes disclosed in WO-A-9744036. For example, a compound of formula (i) may be prepared by treating the free base with peracetic acid in acetic acid in an appropriate solvent such as chloroform, or with hydrogen peroxide in acetic acid.

The invention includes the prevention and treatment of TNF mediated disease or disease states, by which is meant any and all disease states in which TNF plays a role, either by production of TNF itself, or by TNF causing another cytokine to be released,

such as but not limited to IL-1 or IL-6. A disease state in which IL-1, for instance, is a major component, and whose production or action is exacerbated or secreted in response to TNF, would therefore be considered a disease state mediated by TNF. As TNF-β (also known as lymphotoxin) has close structural homology with TNF-α (also known as cachectin), and since each induces similar biological responses and binds to the same cellular receptor, both TNF-α and TNF-β are inhibited by compounds of the present invention and thus are herein referred to collectively as "TNF" unless specifically delineated otherwise.

PDE IV inhibitors are useful in the treatment of a variety of allergic and inflammatory diseases, including: asthma, chronic bronchitis, atopic dermatitis, atopic eczema, urticaria, allergic rhinitis, allergic conjunctivitis, vernal conjunctivitis, inflammation of the eye, allergic responses in the eye, eosinophilic granuloma, psoriasis, Bechet's disease, erythematosis, anaphylactoid purpura nephritis, joint inflammation, arthritis, rheumatoid arthritis and other arthritic conditions such as rheumatoid spondylitis and osteoarthritis, septic shock, ulcerative colitis, Crohn's disease, reperfusion injury of the myocardium and brain, chronic glomerulonephritis, endotoxic shock and adult respiratory distress syndrome. In addition, PDE IV inhibitors are useful in the treatment of diabetes insipidus and conditions associated with cerebral metabolic inhibition, such as cerebral senility, senile dementia (Alzheimer's disease), memory impairment associated with Parkinson's disease, depression and multi-infarct dementia. PDE IV inhibitors are also useful in conditions ameliorated by neuroprotectant activity, such as cardiac arrest, stroke and intermittent claudication. Additionally, PDE IV inhibitors could have utility as gastroprotectants. A special embodiment of the therapeutic methods of the present invention is the treatment of asthma.

The viruses contemplated for treatment herein are those that produce TNF as a result of infection, or those which are sensitive to inhibition, such as by decreased replication, directly or indirectly, by the TNF inhibitors of Formula (i). Such viruses include, but are not limited to HIV-1, HIV-2 and HIV-3, cytomegalovirus (CMV), influenza, adenovirus and the Herpes group of viruses, such as, but not limited to, *Herpes zoster* and *Herpes simplex*.

This invention more specifically relates to a method of treating a mammal, afflicted with a human immunodeficiency virus (HIV), which comprises administering to such

mammal an effective TNF inhibiting amount of a compound of Formula (i) or a pharmaceutically-acceptable salt thereof.

The compounds of this invention may be also be used in association with the veterinary treatment of animals, other than humans, in need of inhibition of TNF production. TNF mediated diseases for treatment, therapeutically or prophylactically, in animals include disease states such as those noted above, but in particular viral infections. Examples of such viruses include, but are not limited to feline immunodeficiency virus (FIV) or other retroviral infection such as equine infectious anaemia virus, caprine arthritis virus, visna virus, maedi virus and other lentiviruses.

The compounds of this invention are also useful in treating parasite, yeast and fungal infections, where such yeast and fungi are sensitive to upregulation by TNF or will elicit TNF production *in vivo*. A preferred disease state for treatment is fungal meningitis.

The compounds of formula (i) are preferably in pharmaceutically-acceptable form. By pharmaceutically-acceptable form is meant, *inter alia*, a pharmaceutically-acceptable level of purity excluding normal pharmaceutical additives such as diluents and carriers, and including no material considered toxic at normal dosage levels. A pharmaceutically-acceptable level of purity will generally be at least 50% excluding normal pharmaceutical additives, preferably 75%, more preferably 90% and still more preferably 95%. When used herein the term "pharmaceutically-acceptable" encompasses materials suitable for both human and veterinary use.

A compound of formula (i) or where appropriate a pharmaceutically-acceptable salt thereof and/or a pharmaceutically-acceptable solvate thereof, may be administered *per se* or, preferably, as a pharmaceutical composition also comprising a pharmaceutically-acceptable carrier.

Accordingly, the present invention provides a pharmaceutical composition comprising a compound of formula (i) or where appropriate a pharmaceutically-acceptable salt thereof and/or a pharmaceutically-acceptable solvate thereof, and a pharmaceutically-acceptable carrier.

The active compound may be formulated for administration by any suitable route, the preferred route depending upon the disorder for which treatment is required, and is preferably in unit dosage form or in a form that a human patient may administer to himself in a single dosage. Advantageously, the composition is suitable for oral, rectal, topical,

parenteral administration or through the respiratory tract. Preparations may be designed to give slow release of the active ingredient.

The term parenteral as used herein includes subcutaneous injections, intravenous, intramuscular, intrasternal injection or infusion techniques. In addition to the treatment of warm-blooded animals such as mice, rats, horses, cattle, sheep, dogs, cats, etc, the compounds of the invention are effective in the treatment of humans.

The compositions of the invention may be in the form of tablets, capsules, sachets, vials, powders, granules, lozenges, suppositories, reconstitutable powders, or liquid preparations such as oral or sterile parenteral solutions or suspensions. Topical formulations are also envisaged where appropriate.

In order to obtain consistency of administration it is preferred that a composition of the invention is in the form of a unit dose. Unit dose presentation forms for oral administration may be tablets and capsules and may contain conventional excipients such as binding agents, for example syrup, acacia, gelatin, sorbitol, tragacanth, or polyvinylpyrrolidone; fillers for example microcrystalline cellulose, lactose, sugar, maize-starch, calcium phosphate, sorbitol or glycine; tabletting lubricants, for example magnesium stearate; disintegrants, for example starch, polyvinylpyrrolidone, sodium starch glycollate or microcrystalline cellulose; or pharmaceutically-acceptable wetting agents such as sodium lauryl sulphate.

Solid oral compositions may be prepared by conventional methods of blending, filling, tabletting or the like. Repeated blending operations may be used to distribute the active agent throughout those compositions employing large quantities of fillers.

Such operations are of course conventional in the art. The tablets may be coated according to methods well known in normal pharmaceutical practice, in particular with an enteric coating.

Oral liquid preparations may be in the form of, for example, emulsions, syrups or elixirs, or may be presented as a dry product for reconstitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, for example sorbitol, syrup, methyl cellulose, gelatin, hydroxyethylcellulose, carboxymethylcellulose, aluminium stearate gel, hydrogenated edible fats; emulsifying agents, for example lecithin, sorbitan monooleate, or acacia, non-aqueous vehicles (which may include edible oils), for example almond oil, fractionated

coconut oil, oily esters such as esters of glycerine, propylene glycol, or ethyl alcohol; preservatives, for example methyl or propyl p-hydroxybenzoate or sorbic acid; and if desired conventional flavouring or colouring agents.

Compositions may also suitably be presented for administration to the respiratory tract as a snuff or an aerosol or solution for a nebuliser, or as a microfine powder for insufflation, alone or in combination with an inert carrier such as lactose. In such a case the particles of active compound suitably have diameters of less than 50 μm, such as from 0.1 to 50 μm, preferably less than 10 μm, for example from 1 to 10 μm, 1 to 5 μm or from 2 to 5 μm. Where appropriate, small amounts of other anti-asthmatics and bronchodilators for example sympathomimetic amines such as isoprenaline, isoetharine, salbutamol, phenylephrine and ephedrine; corticosteroids such as prednisolone and adrenal stimulants such as ACTH may be included.

For parenteral administration, fluid unit dosage forms are prepared utilizing the compound and a sterile vehicle, and, depending on the concentration used, can be either suspended or dissolved in the vehicle. In preparing solutions, the compound can be dissolved in water for injection and filter-sterilised before filling into a suitable vial or ampoule and sealing.

Advantageously, adjuvants such as a local anaesthetic, a preservative and buffering agents can be dissolved in the vehicle. To enhance the stability, the composition can be frozen after filling into the vial and the water removed under vacuum. Parenteral suspensions are prepared in substantially the same manner, except that the compound is suspended in the vehicle instead of being dissolved, and sterilisation cannot be accomplished by filtration. The compound can be sterilised by exposure to ethylene oxide before suspending in the sterile vehicle. Advantageously, a surfactant or wetting agent is included in the composition to facilitate uniform distribution of the compound.

The compositions may contain from 0.1% to 99% by weight, preferably from 10-60% by weight, of the active material, depending on the method of administration.

Compounds of formula (i), or if appropriate a pharmaceutically-acceptable salt thereof and/or a pharmaceutically-acceptable solvate thereof, may also be administered as a topical formulation in combination with conventional topical excipients.

Topical formulations may be presented as, for instance, ointments, creams or lotions, impregnated dressings, gels, gel sticks, spray and aerosols, and may contain

appropriate conventional additives such as preservatives, solvents to assist drug penetration and emollients in ointments and creams. The formulations may contain compatible conventional carriers, such as cream or ointment bases and ethanol or oleyl alcohol for lotions.

Suitable cream, lotion, gel, stick, ointment, spray or aerosol formulations that may be used for compounds of formula (i) or if appropriate a pharmaceutically-acceptable salt thereof, are conventional formulations well known in the art, for example, as described in standard text books such as Harry's Cosmeticology published by Leonard Hill Books, Remington's Pharmaceutical Sciences, and the British and US Pharmacopoeias.

Suitably, the compound of formula (i), or if appropriate a pharmaceutically-acceptable salt thereof, will compromise from about 0.5 to 20% by weight of the formulation, favourably from about 1 to 10%, for example 2 to 5%.

The dose of the compound used in the treatment of the invention will vary in the usual way with the seriousness of the disorders, the weight of the sufferer, and the relative efficacy of the compound. However, as a general guide suitable unit doses may be 0.1 to 1000 mg, such as 0.5 to 200, 0.5 to 100 or 0.5 to 10 mg, for example 0.5, 1, 2, 3, 4 or 5 mg; and such unit doses may be administered more than once a day, for example 2, 3, 4, 5 or 6 times a day, but preferably 1 or 2 times per day, so that the total daily dosage for a 70 kg adult is in the range of about 0.1 to 1000 mg, that is in the range of about 0.001 to 20 mg/kg/day, such as 0.007 to 3, 0.007 to 1.4, 0.007 to 0.14 or 0.01 to 0.5 mg/kg/day, for example 0.01, 0.02, 0.04, 0.05, 0.06, 0.08, 0.1 or 0.2 mg/kg/day, and such therapy may extend for a number of weeks or months.

Assay Methods

The assays used to confirm the phosphodiesterase IV inhibitory activity of compounds of formula (I) are standard assay procedures as disclosed by Schilling *et al*, Anal. Biochem. 216:154 (1994), Thompson and Strada, Adv. Cycl. Nucl. Res. 8:119 (1979) and Gristwood and Owen, Br. J. Pharmacol. 87:91P (1986).

Compounds of formula (i) have exhibited activity at levels consistent with those believed to be useful in treating phosphodiesterase IV related disease states in those assays.

The ability of compounds of formula (i) to inhibit TNF production in human peripheral blood mononuclear cells (PMBC's) is measured as follows. PMBC's are

prepared from freshly taken blood or "Buffy coats" by standard procedures. Cells are plated out in RPMI1640 + 1% foetal calf serum in the presence and absence of inhibitors. LPS (Lipopolysaccharide (endotoxin); 100 ng/ml) is added and cultures are incubated for 22 h at 37°C in an atmosphere of 95% air/5% CO_2. Supernatants are tested for TNFα by ELISA (Enzyme linked immunosorbent assay) using commercially available kits.

Abbreviations

Activity in a guinea pig lung model is measured using the procedures described by Mauser *et al*, Am. Rev. Respir. Dis. 148:1623 (1993), and Am. J. Respir. Crit. Care Med. 152:467 (1995).

The pharmacokinetic profile of the compounds of the invention is determined in rats cannulated in the right carotid artery for blood collection. For iv dosing, the compound is prepared in a suitable formulation, for example 10% v/v DMSO, 50% v/v PEG 400 in water, and dosing is carried out by cannulation of the left jugular vein. Samples are collected at 5min, 0.5, 1, 2, 4, 6 and 8 hours post-dosing. For oral dosing, the compound is prepared in a suitable formulation such as 0.4% w/v methylcellulose in water. Samples are collected at 0.5, 1, 2, 4, 6 and 8 hours post-dosing. In some cases, samples are also collected at 12 hours post-dosing. Plasma is obtained by centrifugation of the each blood sample and drug concentration is then determined using standard methods, such as liquid chromatography-mass spectrometry following protein precipitation.

Results are tabulated below, and are also shown in the accompanying drawing. The drawing is a graph of PK data following oral dosing in the rat; PC (plasma concentration; ng/ml) is plotted against t (time; hours). ■ represents the compound of Example 8, and • the free base. The superiority of the novel compound is evident.

	Example 8	Free base
Dose (iv) (mg/kg)	1	1
Dose (po) (mg/kg)	3	3
Cmax (po) (ng/ml)	3054	1008
$AUC_{0\text{-last}}$ (po) (ng.h/ml)	30169	6860
$t_{1/2}$ (po) (h)	20	4.5

The solubility of the compound of Example 8, in water at pH 7, was 0.2 mg/ml. The solubility of the corresponding free base, under the same conditions, was 0.002 mg/ml. Other exemplified compounds exhibit desirable solubility.

The following Examples illustrate the invention.

Intermediate 1 **2-Trifluoromethylquinolin-8-ol**

A solution of 8-methoxy-2-trifluoromethylquinoline (10.0g) in 48% hydrobromic acid (40ml) was stirred at reflux overnight. The reaction mixture was poured into water (200ml) and the pH adjusted to 12.5 using 46-48% sodium hydroxide solution. After extraction with dichloromethane (2x25ml) the aqueous layer was acidified to pH5.3 by the addition of 37% hydrochloric acid solution. The mixture was then extracted using dichloromethane (2x100ml) and the combined organic extracts washed with water, dried over sodium sulfate, filtered and the solvent removed *in vacuo* to give the product (9.3g) as a white solid.

M.S. [M+H] 214

Intermediate 2 **8-(*Tert*-butyldimethylsilanyloxy)-2-trifluoromethylquinoline**

A solution of 2-trifluoromethylquinolin-8-ol (11.5g), *tert*-butyldimethylsilyl chloride (8.9g) and triethylamine (6.5g) in dichloromethane (60ml) was stirred overnight at room temperature. The reaction mixture was washed with water (2x50ml), dried over sodium sulfate, filtered and the solvent removed *in vacuo* to give the product (17.9g) as a white solid.

M.S. [M+H] 328

The following Intermediate was prepared by a similar procedure.

Intermediate 3 **8-(*Tert*-butyldimethylsilanyloxy)-2-methylquinoline**

Prepared from 8-hydroxyquinaldine (10g) to give the product (17g) as an orange oil.

TLC R_f 0.90 (10% methanol in ethyl acetate)

Intermediate 4 **5-Bromo-8-(*tert*-butyldimethylsilanyloxy)-2-trifluoromethylquinoline**

A solution of 8-(*tert*-butyldimethylsilanyloxy)-2-trifluoromethylquinoline (17.5g) in dichloromethane (100ml) was treated with *N*-bromosuccinimide (10.5g) at 15 °C. The mixture was stirred at 20 °C for 25 minutes, washed with 1% sodium sulfite solution

(100ml), and water (50ml). The organic layer was separated, dried over magnesium sulfate, filtered and the solvent removed *in vacuo* to give the product (21.4g) as a dark oil.

M.S. [M+H] 406

The following Intermediate was prepared by a similar procedure.

Intermediate 5 **5-Bromo-8-(*tert*-butyldimethylsilanyloxy)-2-methylquinoline**

Prepared from 8-(*tert*-butyldimethylsilanyloxy)-2-methylquinoline (0.63g) to give the product (0.66g) as a yellow oil.

TLC R_f 0.90 (dichloromethane)

Intermediate 6 **5-Bromo-2-trifluoromethylquinolin-8-ol**

A solution of 5-bromo-8-(*tert*-butyldimethylsilanyloxy)-2-trifluoromethylquinoline (21g) in methanol (150ml) was treated with 37% hydrochloric acid solution (5ml) and water (5ml). The mixture was stirred for 12h at room temperature and at 45°C for 2h. The methanol was removed *in vacuo* and the residue partitioned between 10% sodium hydroxide solution (100ml) and dichloromethane (50ml). The aqueous layer was neutralised with 37% hydrochloric acid solution to pH7.2 and extracted with dichloromethane (4x50ml). The combined organic extracts were dried over magnesium sulfate, filtered and the solvent removed *in vacuo* to give the product (12g) as a cream solid.

M.S. [M+] 292

Intermediate 7 **5-Bromo-2-methylquinolin-8-ol**

A solution of 5-bromo-8-(*tert*-butyldimethylsilanyloxy)-2-methylquinoline (16.3g) in tetrahydrofuran (500ml) was treated dropwise with a solution of tetrabutylammonium fluoride (1.0M in tetrahydrofuran, 54ml). The mixture was stirred for 10 minutes, diluted with dichloromethane (750ml) and washed with water (3x250ml). The organic solution was dried over magnesium sulphate, filtered and the solvent removed *in vacuo* to give an orange oil. Recrystallisation from aqueous methanol gave the product (7.65g) as a white solid.

TLC R_f 0.58 (10% methanol in dichloromethane).

Intermediate 8 **5-Bromo-8-difluoromethoxy-2-trifluoromethylquinoline**

To a stirred solution of 5-bromo-2-trifluoromethylquinolin-8-ol (12.0g) in dioxane (120ml) was added 47% sodium hydroxide solution (12ml). The mixture was heated to 78°C and chlorodifluoromethane (7.4g) was bubbled through the reaction over 3h. On

cooling, the mixture was diluted with water (80ml) and the solvent removed *in vacuo*. The resulting slurry was filtered and the filter cake washed with dichloromethane (50ml) then water (50ml). The organic layer was separated and the aqueous layer extracted with dichloromethane (50ml). The combined organic extracts were washed with 0.5% sodium hydroxide solution (100ml), dried over magnesium sulfate, filtered and the solvent removed *in vacuo*. The residue was taken up in *tert*-butyl methyl ether (100ml), the cloudy solution filtered and the solvent removed *in vacuo* to give the product (11.7g) as an off white solid.

M.S [M+H] 342

The following Intermediate was prepared by a similar procedure.

Intermediate 9 **5-Bromo-8-difluoromethoxy-2-methylquinoline**

Prepared from 5-bromo-2-methylquinolin-8-ol (1.0g) to give a brown solid. Purification by recrystallisation from methanol gave the product (0.96g) as an off white solid.

TLC R_f 0.86 (50% ethyl acetate in hexane)

Intermediate 10 **8-Difluoromethoxy-2-trifluoromethylquinoline-5-carboxylic acid**

A mixture of 5-bromo-8-difluoromethoxy-2-trifluoromethylquinoline (6.0g), triphenylphosphine (0.3g), bis(triphenylphosphine)palladium (II) chloride (0.15g), 47% sodium hydroxide solution (4.5g) and water (12ml) in tetrahydrofuran (50ml) was purged with carbon monoxide gas in a Parr pressure reactor at 7 bar. This was heated to 100°C for 24h. After cooling and venting the reaction mixture was partitioned between sodium hydroxide solution (1.5g in 50ml) and *tert*-butyl methyl ether (100ml). The organic solution was extracted with sodium hydroxide solution (2x1.5g in 50ml). The combined aqueous extracts were stirred with activated charcoal (1.5g) for 15 minutes and then filtered. The filtrate was acidified to pH4 using 37% hydrochloric acid solution and the resultant cream precipitate isolated by filtration and washed with water (20ml). The crude product was purified by recrystallisation from toluene to give the product (1.8g) as a cream solid.

M.S [M+H] 308

The following Intermediate was prepared by a similar procedure.

Intermediate 11 **8-Difluoromethoxy-2-methylquinoline-5-carboxylic acid**

Prepared from 5-bromo-8-difluoromethoxy-2-methylquinoline (5.72g) to give the product (2.88g) as a brown solid.

TLC R_f 0.60 (10% methanol in dichloromethane)

Intermediate 12 **8-Difluoromethoxy-2-trifluoromethylquinoline-5-carboxylic acid 4-nitrophenyl ester**

A solution of 8-difluoromethoxy-2-trifluoromethylquinoline-5-carboxylic acid (0.5g) in dichloromethane (50ml) was treated with 4-nitrophenol (0.25g), 4-dimethylaminopyridine (catalytic) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (0.35g) and the mixture was stirred at room temperature for 12h. The reaction was washed with water (50ml), dried over sodium sulphate, filtered and the solvent removed *in vacuo*. The residue was purified by column chromatography on silica eluting with dichloromethane to give the product (0.47g) as a cream solid.

TLC R_f 0.75 (5% ethyl acetate in dichloromethane).

The following Intermediates were prepared by a similar procedure.

Intermediate 13 **8-Difluoromethoxy-2-methylquinoline-5-carboxylic acid 4-nitrophenyl ester**

Prepared from 8-difluoromethoxy-2-methylquinoline-5-carboxylic acid (0.50g). Purification by column chromatography on silica eluting with 50% ethyl acetate in hexane gave the product (0.63g) as yellow solid.

TLC R_f 0.73 (10% methanol in dichloromethane)

Intermediate 14 **8-Methoxy-2-trifluoromethylquinoline-5-carboxylic acid 4-nitrophenyl ester**

Prepared from 8-methoxy-2-trifluoromethylquinoline-5-carboxylic acid (0.60g) to give the title compound (0.75g) as a yellow solid.

TLC R_f 0.64 (50% ethyl acetate in hexane)

Intermediate 15 **8-Difluoromethoxy-2-methylquinoline-5-carboxylic acid (3-chloropyridin-4-yl)amide**

To a stirred solution of 4-amino-3-chloropyridine (136mg) in *N,N*-dimethylformamide (2ml) under an atmosphere of nitrogen was added sodium hydride (60% dispersion in oil, 42mg). The reaction mixture was stirred at room temperature for

1h. 8-Difluoromethoxy-2-methylquinoline-5-carboxylic acid 4-nitrophenyl ester (200mg) was then added and stirring continued for 18h. The solvent was removed *in vacuo* and the resulting residue purified by column chromatography on silica eluting with 50% ethyl acetate in hexane to give the product (155mg) as a white solid.

TLC R_f 0.3 (50% ethyl acetate in hexane)

The following Intermediates were prepared by a similar procedure.

Intermediate 16 **8-Difluoromethoxy-2-methylquinoline-5-carboxylic acid (3-methylpyridin-4-yl)amide**

Prepared from 8-difluoromethoxy-2-methylquinoline-4-carboxylic acid 4-nitrophenyl ester (500mg) and 4-amino-3-methylpyridine (170mg). Purification by column chromatography on silica eluting with 10% methanol in dichloromethane gave the product (200mg) as a pale yellow solid.

TLC R_f 0.55 (10% methanol in ethyl acetate)

Intermediate 17 **8-Difluoromethoxy-2-trifluoromethylquinoline-5-carboxylic acid (3-chloropyridin-4-yl)amide**

Prepared from 8-difluoromethoxy-2-trifluoromethylquinoline-5-carboxylic acid 4-nitrophenyl ester (466mg) and 4-amino-3-chloropyridine (283mg). Purification by column chromatography on silica eluting with 15% ethyl acetate in dichloromethane gave the product (297mg) as a white solid.

TLC R_f 0.26 (15% ethyl acetate in dichloromethane)

Intermediate 18 **8-Difluoromethoxy-2-trifluoromethylquinoline-5-carboxylic acid (3,5-dichloropyridin-4-yl)amide**

Prepared from 8-difluoromethoxy-2-trifluoromethylquinoline-5-carboxylic acid 4-nitrophenyl ester (480mg) and 4-amino-3,5-dichloropyridine (360mg). Purification by column chromatography on silica eluting with 20% ethyl acetate in hexane gave the product (424mg) as a white solid.

TLC R_f 0.42 (20% ethyl acetate in hexane)

Intermediate 19 **8-Difluoromethoxy-2-trifluoromethylquinoline-5-carboxylic acid (3,5-difluoropyridin-4-yl)amide**

Prepared from 8-difluoromethoxy-2-trifluoromethylquinoline-5-carboxylic acid 4-nitrophenyl ester (390mg) and 4-amino-3,5-difluoropyridine (120mg). Purification by

column chromatography on silica eluting with 10% ethyl acetate in dichloromethane gave the product (180mg) as a white solid.

TLC R_f 0.27 (15% ethyl acetate in dichloromethane)

Intermediate 20 **8-Methoxy-2-trifluoromethylquinoline-5-carboxylic acid (3,5-difluoropyridin-4-yl)amide**

Prepared from 8-methoxy-2-trifluoromethylquinoline-5-carboxylic acid 4-nitrophenyl ester (425mg) and 4-amino-3,5-difluoropyridine (282mg). Purification by column chromatography on silica eluting with 5% methanol in dichloromethane gave the product (162mg) as a white solid.

TLC R_f 0.34 (5% methanol in dichloromethane)

Intermediate 21 **8-Methoxy-2-trifluoromethylquinoline-5-carboxylic acid (3-chloropyridin-4-yl)amide**

To a stirred solution of 4-amino-3-chloropyridine (124mg) in *N,N*-dimethylformamide (5ml) under an atmosphere of nitrogen was added sodium hydride (60% dispersion in oil, 52mg). The reaction mixture was stirred at room temperature for 1h. 8-Methoxy-2-trifluoromethylquinoline-4-carbonyl chloride (360mg) was then added and stirring continued for 18h. The solvent was removed *in vacuo* and the resulting residue partitioned between ethyl acetate (2x50ml) and water (50ml). The organic layer was separated, dried over magnesium sulphate, filtered and the solvent removed *in vacuo*. Purification by column chromatography on silica eluting with ethyl acetate gave the product (330mg) as a pale pink solid.

TLC R_f 0.41 (ethyl acetate)

mp 192-194°C

The following Intermediate was prepared by a similar procedure.

Intermediate 22 **8-Methoxy-2-trifluoromethylquinoline-5-carboxylic acid (3-methylpyridin-4-yl)amide**

Prepared from 8-methoxy-2-trifluoromethylquinoline-4-carbonyl chloride (430mg) and 4-amino-3-methylpyridine (170mg). Purification by column chromatography eluting with 10% methanol in ethyl acetate gave the product (160mg) as a white solid.

TLC R_f 0.29 (10% methanol in ethyl acetate)

Intermediate 23 **8-Difluoromethoxy-2-trifluoromethylquin line-5-carboxylic acid (3-methylpyridin-4-yl)amide**

A solution of 8-difluoromethoxy-2-trifluoromethylquinoline-4-carboxylic acid (0.50g) in dichloromethane (30ml) was stirred at room temperature under an atmosphere of nitrogen. Oxalyl chloride (0.28ml) was added followed by *N,N*-dimethylformamide (1 drop) and stirring continued overnight. The solvent was removed *in vacuo* to give 8-difluoromethoxy-2-trifluoromethylquinoline-4-carbonyl chloride (650mg) as an off white solid.

To a stirred solution of 8-difluoromethoxy-2-trifluoromethylquinoline-4-carbonyl chloride (650mg) in dichloromethane (40ml) under an atmosphere of nitrogen was added triethylamine (0.68ml) and 4-amino-3-methylpyridine (352mg). The reaction mixture was stirred for 18h. The solvent was removed *in vacuo* and the resulting residue purified by column chromatography on silica eluting with 5% methanol in dichloromethane to give the product (563mg) as a pale white solid.

TLC R_f 0.53 (10% methanol in dichloromethane)

The following Intermediate was prepared by a similar procedure

Intermediate 24 **8-Methoxy-2-trifluoromethylquinoline-5-carboxylic acid (3,5-dimethylpyridin-4-yl)amide**

Prepared from 8-methoxy-2-trifluoromethylquinoline-4-carbonyl chloride (500mg) and 4-amino-3,5-dimethylpyridine (210mg). Purification by trituration with acetone and ether gave the product (82mg) as a pale yellow solid.

TLC R_f 0.42 (10% methanol in dichloromethane with 1% ammonium hydroxide)

Example 1 **8-Difluoromethoxy-2-methylquinoline-5-carboxylic acid (3-chloro-1-oxypyridin-4-yl)amide**

Peracetic acid (36-40% in acetic acid, 0.1ml) was added to a solution of 8-difluoromethoxy-2-methylquinoline-5-carboxylic acid (3-chloropyridin-4-yl)amide (50mg) in chloroform (10ml) at room temperature. After stirring overnight the reaction was diluted with dichloromethane (20ml) and washed with water (20ml). The organic phase was dried over magnesium sulfate and the solvent removed *in vacuo* to give a white solid. Purification by column chromatography eluting with 10% methanol in ethyl acetate gave the product (25mg) as a white solid.

TLC R_f 0.2 (10% methanol in ethyl acetate)

mp 244°C (dec.)

The following Examples were prepared by a similar procedure.

Example 2 **8-Difluoromethoxy-2-trifluoromethylquinoline-5-carboxylic acid (3-chloro-1-oxypyridin-4-yl)amide**

Prepared from 8-difluoromethoxy-2-trifluoromethylquinoline-5-carboxylic acid (3-chloropyridin-4-yl)amide (261mg) to give the product (223mg) as a cream solid.

TLC R_f 0.4 (ethyl acetate)

mp 212-213°C

Example 3 **8-Methoxy-2-trifluoromethylquinoline-5-carboxylic acid (3-chloro-1-oxypyridin-4-yl)amide**

Prepared from 8-methoxy-2-trifluoromethylquinoline-5-carboxylic acid (3-chloropyridin-4-yl)amide (50mg) to give the product (25mg) as an off white solid.

TLC R_f 0.7 (10% methanol in ethyl acetate)

mp 261.5-262.5°C

Example 4 **8-Methoxy-2-trifluoromethylquinoline-5-carboxylic acid (3,5-difluoro-1-oxypyridin-4-yl)amide**

Prepared from 8-methoxy-2-trifluoromethylquinoline-5-carboxylic acid (3,5-difluoropyridin-4-yl)amide (120mg) with stirring at room temperature for two weeks. Excess peracetic acid (4x0.5ml) was added over this period. Purification by column chromatography eluting with 5-10% methanol in dichloromethane gave the product (28mg) as a yellow solid.

TLC R_f 0.09 (5% methanol in dichloromethane)

mp 268-269°C (dec.)

Example 5 **8-Difluoromethoxy-2-trifluoromethylquinoline-5-carboxylic acid (3,5-difluoro-1-oxypyridin-4-yl)amide**

Prepared from 8-difluoromethoxy-2-trifluoromethylquinoline-5-carboxylic acid (3,5-difluoropyridin-4-yl)amide (160mg) with stirring at room temperature for two weeks. Excess peracetic acid (3x0.1ml) was added over this period. Purification by column chromatography eluting with 15% ethyl acetate in dichloromethane increasing to 10% methanol in dichloromethane gave the product (120mg) as a yellow solid.

TLC R_f 0.69 (2% methanol in dichloromethane)

mp 219-220°C

Example 6 **8-Difluoromethoxy-2-trifluoromethylquinoline-5-carboxylic acid (3-methyl-1-oxypyridin-4-yl)amide**

Prepared from 8-difluoromethoxy-2-trifluoromethylquinoline-5-carboxylic acid (3-methylpyridin-4-yl)amide (316mg) stirred in the presence of peracetic acid (2x0.18ml) for two days. Purification by column chromatography eluting with 10% methanol in dichloromethane gave the product (267mg) as a white solid.

TLC R_f 0.25 (10% methanol in dichloromethane)

mp 210-212°C

Example 7 **8-Methoxy-2-trifluoromethylquinoline-5-carboxylic acid (3,5-dimethyl-1-oxypyridin-4-yl)amide**

Prepared from 8-methoxy-2-trifluoromethylquinoline-5-carboxylic acid (3,5-dimethylpyridin-4-yl)amide (56mg) stirred in the presence of peracetic acid (2x 0.05ml) for two days. Purification by column chromatography eluting with 1% ammonium hydroxide/10% methanol in dichloromethane gave the product (37mg) as a white solid.

TLC R_f 0.22 (1% ammonium hydroxide/10% methanol in dichloromethane)

mp 237-239°C

Example 8 **8-Methoxy-2-trifluoromethylquinoline-5-carboxylic acid (3,5-dichloro-1-oxypyridin-4-yl)amide**

8-Methoxy-2-trifluoromethylquinoline-5-carboxylic acid (3,5-dichloropyridin-4-yl)amide (200mg) was stirred in the presence of peracetic acid (36-40% in acetic acid, 0.1ml) in chloroform at 50°C for 5 days. Additional peracetic acid (0.1ml) was added and the reaction heated for a further 2 days. Purification by column chromatography eluting with 10% methanol in ethyl acetate gave the product (123mg) as a white solid.

TLC R_f 0.17 (10% methanol in ethyl acetate)

mp 280-281°C

Example 9 **8-Difluoromethoxy-2-trifluoromethylquinoline-5-carboxylic acid (3,5-dichloro-1-oxypyridin-4-yl)amide**

Prepared from 8-difluoromethoxy-2-trifluoromethylquinoline-5-carboxylic acid (3,5-dichloropyridin-4-yl)amide (415mg) in a similar manner to 8-methoxy-2-trifluoromethyl-quinoline-5-carboxylic acid (3,5-dichloro-1-oxy-pyridin-4-yl)-amide. Purification by column chromatography eluting with 1% ammonium hydroxide/10% methanol in dichloromethane afforded the title compound as a cream solid (360mg).

TLC R_f 0.5 (1% ammonium hydroxide/10% methanol in dichloromethane)

mp 244-245°C

Example 10 **8-Difluoromethoxy-2-methylquinoline-5-carboxylic acid (3-methyl-1-oxypyridin-4-yl)amide**

Sodium hydride (60% dispersion in oil, 0.11g) was added to a stirred solution of 3-methyl-1-oxypyridin-4-ylamine (0.2g) in *N,N*-dimethylformamide (10ml) under nitrogen at room temperature in the presence of molecular sieves. After stirring for one hour 8-difluoromethoxy-2-methylquinoline-5-carboxylic acid 4-nitrophenyl ester was added and the reaction stirred overnight. The solvent was removed *in vacuo* and the residue partitioned between ethyl acetate (50ml) and water (2x50ml). The organic phase was dried over magnesium sulfate and concentrated *in vacuo*. The residue was washed with a little ethyl acetate and dried to give the product (50mg) as a pale yellow solid.

TLC R_f 0.27 (1% triethylamine/20% methanol in dichloromethane)

mp 231.5-233.5°C

Example 11 **8-Methoxy-2-trifluoromethylquinoline-5-carboxylic acid (3-methyl-1-oxypyridin-4-yl)amide**

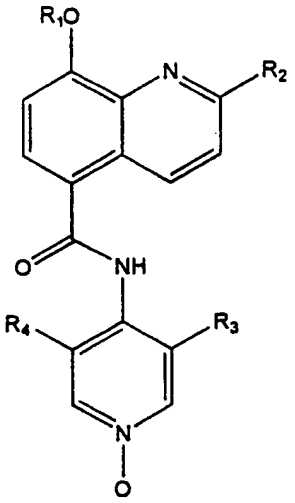
Triethylamine (0.55ml) and 4-dimethylaminopyridine (catalytic) were added to a stirred suspension of 3-methyl-1-oxypyridin-4-ylamine (0.23g) in dichloromethane (40ml) under nitrogen at room temperature. 8-Methoxy-2-trifluoromethylquinoline-5-carbonyl chloride, hydrochloride salt (0.6g) was added and the reaction stirred overnight. The solvent was removed *in vacuo* and the residue partitioned between ethyl acetate (50ml) and water (3x50ml). The precipitate in the organic phase was filtered off and dried *in vacuo* at 45°C to give the product (0.2g) as a white solid.

TLC R_f 0.12 (ethyl acetate)

mp 249.5-250.5°C

CLAIMS

1. A compound of the formula



(i)

wherein

R_1 is CH_3, CH_2F, CHF_2 or CF_3;

R_2 is CH_3 or CF_3;

R_3 is F, Cl, Br, CN or CH_3; and

R_4 is H, F, Cl, Br, CN or CH_3;

or a pharmaceutically-acceptable salt thereof.

2. A compound of claim 1, selected from

8-difluoromethoxy-2-methylquinoline-5-carboxylic acid (3-chloro-1-oxypyridin-4-yl)amide,

8-difluoromethoxy-2-trifluoromethylquinoline-5-carboxylic acid (3-chloro-1-oxypyridin-4-yl)amide,

8-methoxy-2-trifluoromethylquinoline-5-carboxylic acid (3-chloro-1-oxypyridin-4-yl)amide,

8-methoxy-2-trifluoromethylquinoline-5-carboxylic acid (3,5-difluoro-1-oxypyridin-4-yl)amide,

8-difluoromethoxy-2-trifluoromethylquinoline-5-carboxylic acid (3,5-difluoro-1-oxypyridin-4-yl)amide,

8-difluoromethoxy-2-trifluoromethylquinoline-5-carboxylic acid (3-methyl-1-oxypyridin-4-yl)amide,

8-methoxy-2-trifluoromethylquinoline-5-carboxylic acid (3,5-dimethyl-1-oxypyridin-4-yl)amide,

8-methoxy-2-trifluoromethylquinoline-5-carboxylic acid (3,5-dichloro-1-oxypyridin-4-yl)amide,

8-difluoromethoxy-2-trifluoromethylquinoline-5-carboxylic acid (3,5-dichloro-1-oxypyridin-4-yl)amide,

8-difluoromethoxy-2-methylquinoline-5-carboxylic acid (3-methyl-1-oxypyridin-4-yl)amide, and

8-methoxy-2-trifluoromethylquinoline-5-carboxylic acid (3-methyl-1-oxypyridin-4-yl)amide.

3. A compound of claim 1, which is 8-methoxy-2-trifluoromethylquinoline-5-carboxylic acid (3,5-dichloro-1-oxypyridin-4-yl)amide.

4. Use of a compound of any preceding claim, for the manufacture of a medicament for use in the treatment of a disease state that is capable of being modulated by inhibition of phosphodiesterase IV or Tumour Necrosis Factor, or that is a pathological condition associated with a function of phosphodiesterase IV, eosinophil accumulation or a function of the eosinophil.

5. The use of claim 4, wherein the disease state is an inflammatory disease or autoimmune disease.

6. The use of claim 4, wherein the disease state is selected from asthma, chronic bronchitis, chronic pulmonary inflammatory disease, chronic obstructive airways disease, atopic dermatitis, allergic rhinitis, psoriasis, arthritis, rheumatoid arthritis, joint inflammation, ulcerative colitis, Crohn's disease, atopic eczema, stroke, bone resorption disease, multiple sclerosis and inflammatory bowel disease.

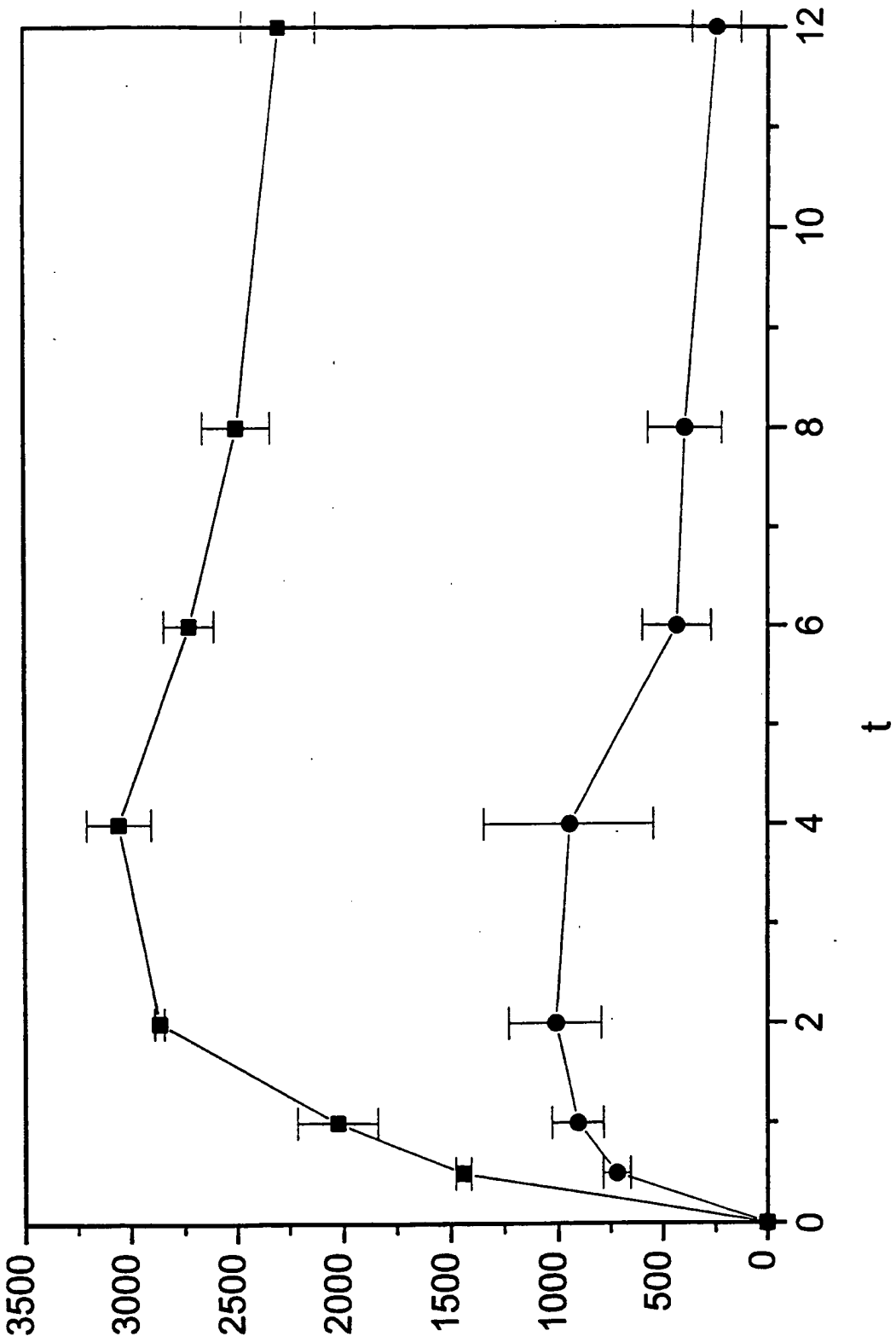
7. The use of claim 4, wherein the disease state is selected from urticaria, allergic conjunctivitis, vernal conjunctivitis, inflammation of the eye, allergic responses in the eye, eosinophilic granuloma, gouty arthritis and other arthritic conditions, adult respiratory distress syndrome, diabetes insipidus, keratosis, cerebral senility, multi-infarct dementia, senile dementia, memory impairment associated with Parkinson's disease, depression, cardiac arrest, intermittent claudication, rheumatoid spondylitis, osteoarthritis, sepsis,

septic shock, endotoxic shock, gram negative sepsis, toxic shock syndrome, acute respiratory distress syndrome, cerebral malaria, silicosis, pulmonary sarcoidosis, reperfusion injury, graft vs host reaction, allograft rejection, infection-related fever or myalgia, malaria, HIV, AIDS, ARC, cachexia, keloid formation, scar tissue formation, pyresis, systemic lupus erythematosus, type 1 diabetes mellitus, Bechet's disease, anaphylactoid purpura nephritis, chronic glomerulonephritis, leukaemia, tarditive dyskinesia, yeast or fungal infection, conditions requiring gastroprotection, and neurogenic inflammatory disease associated with irritation and pain.

8. The use of claim 4, wherein the disease state is asthma.

9. The use of claim 5, wherein the disease state is chronic obstructive airways disease or chronic bronchitis.

10. The use of any of claims 4 to 9, wherein the compound is as defined in claim 3.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INTERNATIONAL SEARCH REPORT

Inter ..nal Application No
PCT/GB 99/03628

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D401/12 A61K31/47 A61P11/06

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 97 44036 A (MONTANA JOHN GARY ;SABIN VERITY MARGARET (GB); DYKE HAZEL JOAN (GB)) 27 November 1997 (1997-11-27) cited in the application claim 8	1-10
Y	REGAN J ET AL: "2-substituted-4-methoxybenzimidazole-based PDE4 inhibitors" BIOORGANIC & MEDICINAL CHEMISTRY LETTERS,GB,OXFORD, vol. 8, no. 19, 6 October 1998 (1998-10-06), pages 2737-2742, XP004139611 ISSN: 0960-894X table 2	1-10

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
1 March 2000	08/03/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax (+31–70) 340–3016	Steendijk, M

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INTERNATIONAL SEARCH REPORT

Intern. ...nal Application No
PCT/GB 99/03628

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	HULME C ET AL: "Orally active indole N-oxide PDE4 inhibitors" BIOORGANIC & MEDICINAL CHEMISTRY LETTERS,GB,OXFORD, vol. 8, no. 21, 3 November 1998 (1998-11-03), pages 3053-3058, XP004141874 ISSN: 0960-894X table 1	1-10
A	WO 97 48697 A (ALDOUS DAVID JOHN ;RHONE POULENC RORER LTD (GB); BOWER SHELLEY (GB)) 24 December 1997 (1997-12-24) claim 33	1-10

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

information on patent family members

Inter. nal Application No
PCT/GB 99/03628

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9744036 A	27-11-1997	AU 2905897 A	09-12-1997
		AU 2905997 A	09-12-1997
		BR 9709015 A	03-08-1999
		BR 9709105 A	03-08-1999
		CN 1219168 A	09-06-1999
		CN 1219131 A	09-06-1999
		CZ 9803651 A	17-03-1999
		EP 0952832 A	03-11-1999
		EP 0912519 A	06-05-1999
		WO 9744322 A	27-11-1997
		NO 985376 A	19-11-1998
		PL 329922 A	26-04-1999
		US 5834485 A	10-11-1998
		US 5804588 A	08-09-1998
WO 9748697 A	24-12-1997	AU 3102697 A	07-01-1998
		CA 2258728 A	24-12-1997
		EP 0934307 A	11-08-1999